1st Invitation to Manufacturers of Biotherapeutic Products (BTPs) and Similar Biotherapeutic Products (SBPs) to Submit an Expression of Interest (EOI) for Product Evaluation to the WHO Prequalification Team - Biotherapeutic Products (BTPs)

To support national and global efforts to increase access to and the affordability of biotherapeutic products (BTPs), and their corresponding similar biotherapeutic products (SBPs), WHO invites manufacturers of selected BTPs and SBPs containing the active ingredient rituximab or trastuzumab to submit Expressions of Interest (EOI) for product evaluation.

1. Procedure for this Invitation to EOI

The current Invitation is published in accordance with the "WHO Pilot Procedure for Prequalification of Biotherapeutic Products: rituximab and trastuzumab" which is available on the WHO website.

Assessment of product(s) submitted under this Invitation for EOI will include, but not be limited to:

- Assessment of product dossiers, which must include product data and information as specified in the relevant guidelines for submission;
- Inspection of manufacturing sites, which must adhere to current good manufacturing practices (cGMP) and good distribution practices (GDP);
- Inspection of clinical sites (if applicable), which must adhere to current good clinical practice (cGCP) and current good laboratory practices (cGLPs).
- Assessment during dossier assessment and/or inspection of ability to meet relevant operational packaging and presentation specifications; and adhere to the principles laid out in the WHO guidelines on the international packaging and shipping of vaccines.

If evaluation demonstrates, as determined by WHO, that a product and its corresponding manufacturing (and clinical) site(s) meet WHO recommended standards, the product (as manufactured at the specified manufacturing site(s)) will be included in the WHO list of prequalified products that are considered to be acceptable, in principle, for procurement by interested United Nations agencies and WHO Member States.

2. Products included in the 1st Invitation

The aim of this 1st EOI is to facilitate access to biotherapeutic products, including similar biotherapeutic products. The recommended active ingredients, dosage forms and strengths listed in this document have been identified by WHO for effective treatment of patients suffering from certain type of cancers. These formulations are included in the WHO Model List of Essential Medicines[1].

Products included in the WHO Model List of Essential Medicines are those which satisfy the priority health care needs of a population. They are selected on the basis of disease prevalence, evidence on efficacy and safety, and comparative cost-effectiveness. [Products included in WHO treatment guidelines are selected on the basis of an assessment of the quality of evidence for benefits, harms, costs, and appropriateness for use in a variety of situations, taking onto account needs of special populations, and the values and preferences of the groups(professional and patient) using them.]

Interested manufacturers are encouraged to submit documentation for the medicinal product used within the approved indication as specified below[2]:

1. Rituximab injection 100 mg/10 mL in 10- mL vial; 500 mg/50 mL in 50- mL (used principally to treat (a) diffuse large B-cell lymphoma, (b) chronic lymphocytic leukaemia or (c) follicular lymphoma)
2. Trastuzumab Powder for injection: 60 mg; 150 mg; 420 mg in vial (used to treat (y) early stage HER2 positive breast cancer or (z) metastatic HER2 positive breast cancer)

[1] WHO Model List of Essential Medicines, 20th List (March 2017, Amended August 2017) http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017_FINAL_amendedAug2017.pdf?ua=1

[2] vials may contain an overage to ensure that the intended dose at the claimed concentration can be withdrawn. For example, vials filled with nominal values of 440mg trastuzumab will be acceptable.

This invitation to EOI is limited to:

- Rituximab or trastuzumab BTPs, or their corresponding SBPs, that have been approved by stringent regulatory authorities (SRA) and marketed in the country of registration; and which will be assessed via an Abridged Assessment pathway according to, among other documents, the "*WHO Pilot Procedure for Prequalification of Biotherapeutic Products: rituximab or trastuzumab*" and the "*WHO Guidelines on submission of documentation for the pilot procedure for prequalification of rituximab or trastuzumab approved by stringent regulatory authorities*".

- Rituximab or trastuzumab SBPs that have been registered by non-SRAs and marketed in the country of registration ; and which will be assessed via a Full Assessment pathway according to, among other documents, the "*WHO Pilot Procedure for Prequalification of Biotherapeutic Products: rituximab or trastuzumab*" and the *"WHO Guidelines on submission of documentation for the pilot procedure for prequalification of similar biotherapeutic products for rituximab and trastuzumab. Preparation of product dossiers in common technical document format"*. A similarity exercise (i.e., a head-to-head comparison of the SBP against a reference biotherapeutic product that, in turn, has been registered/licensed by an SRA on the basis of a full dossier with comprehensive data on non-clinical and clinical studies) will be required.

Article 3. How to submit an EOI

In order to submit an expression of interest for product evaluation, the manufacturer must send the required documentation, arranged according to the information provided on the WHO Prequalification Team website http://www.who.int/medicines/regulation/prequalification/en/. No fees are applicable for this 1st Invitation under the WHO pilot procedure.

Article 4. Quality assessment procedure following submission of an EOI by a manufacturer

The quality assessment is undertaken to determine whether the product being evaluated meets the requirements recommended by WHO, and is manufactured in compliance with current good manufacturing practices (cGMP).

The procedure established by WHO for quality assessment incorporates:

- general understanding of the production and quality control activities of the manufacturer;
- assessment of product data and information on safety, efficacy and quality submitted by the manufacturer, including product formulation, manufacture and test data and results;
- assessment of the manufacturing site's adherence to cGMP and GDP, and its consistency in production and quality control of starting materials, with specific emphasis on active pharmaceutical ingredients, and finished product;
- assessment of clinical testing units or organizations (i.e. parties performing one or more clinical trials with the product) for compliance with current good clinical practice (cGCP) and current good laboratory practices (cGLP), as appropriate;
- random sampling and testing of the products supplied.

Previous evaluation conducted by relevant national regulatory authorities (NRAs) may, in WHO's discretion, be taken into account during the evaluation conducted by WHO, provided that the NRA has expertise in the product area. If appropriate, WHO may collaborate with relevant NRAs regarding the product evaluation. Accordingly, any manufacturer who submits a product for evaluation is therefore encouraged to: (i) request its NRAs to collaborate with WHO in the evaluation process including, in particular, the quality assessment process; and (ii) authorize its NRAs to discuss relevant product files with WHO representatives during assessments and inspections, if required (subject to appropriate confidentiality provisions, if necessary).

Once WHO is satisfied that quality assessment has been completed for the manufacturer of the relevant drug substance, drug product, and the clinical testing units, and that the product meets WHO recommended standards, the product (as produced at the specified manufacturing site) is added to the WHO List of Prequalified Products BTPs.

Article 5. References and further information

For further information on the WHO Prequalification Team please visit PQT website at:
http://www.who.int/medicines/regulation/prequalification/en/

If you have any questions relating to the procedure for responding to an EOI, please write to PQT at its email address: *prequalbiosimilar@who.int*.
Your question(s) will be directed to the prequalification team member who can best advise you.

For further information on the WHO Model List of Essential Medicines, and WHO Expert Committee on the selection and use of Essential Medicine, please visit the Programme's website at:
http://www.who.int/medicines/publications/essentialmedicines/en/
http://www.who.int/selection_medicines/committees/en/

World Health Assembly (WHA) adopted Resolution WHA 67.21 on "Access to biotherapeutic products including similar biotherapeutic products and ensuring their quality, safety and efficacy"
http://www.who.int/medicinedocs/documents/s21459en/s21459en.pdf

WHO guidelines on the international packaging and shipping of vaccines, WHO/IVB/05.23,
http://www.who.int/immunization/documents/WHO_IVB_05.23/en/

WHO Pilot Procedure for Prequalification of Biotherapeutic Products: rituximab and trastuzumab,
http://www.who.int/medicines/regulation/prequalification/01_Pilot_Prequalification_BTPs_June2018.pdf

WHO Guidelines on submission of documentation for the pilot procedure for prequalification of rituximab or trastuzumab approved by stringent regulatory authorities,
http://www.who.int/medicines/regulation/prequalification/03_GLs_Submission_Pilot_AbridgedPathway2018.pdf

WHO Guidelines on submission of documentation for the pilot procedure for prequalification of similar biotherapeutic products for rituximab and trastuzumab. Preparation of product dossiers in common technical document format,
http://www.who.int/medicines/regulation/prequalification/02_GLs_Submission_Pilot_FullPathway_2018.pdf

WHO Model List of Essential Medicines, 20th List March 2017, Amended August 2017
http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017_FINAL_amendedAug2017.pdf?ua=1

WHO Guidelines on evaluation of similar biotherapeutic products (SBPs), Annex 2, Technical Report Series No. 977, 2009,
http://www.who.int/biologicals/publications/trs/areas/biological_therapeutics/TRS_977_Annex_2.pdf

WHO Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs), Annex 2, Technical Report Series No. 1004, 2016,
http://www.who.int/biologicals/biotherapeutics/WHO_TRS_1004_web_Annex_2.pdf

WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology, Annex 4, Technical Report Series No. 987, 2014,
http://www.who.int/biologicals/areas/biological_therapeutics/Annex_3_Regulatory_assessment_of_approved_rDNA-derived_biotherapeutics.pdf

Guidelines for the preparation of a contract research organization master file, Annex 7, Technical Report Series No. 957, 2010,
http://www.who.int/entity/medicines/areas/quality_safety/quality_assurance/GuidelinesPreparationContractResearchOrgMasterfileTRS957Annex7.pdf?ua=1

WHO Guidelines on procedures and data requirements for changes to approved biotherapeutic products, Annex 3, Technical Report Series No. 1011, 2018.
http://www.who.int/biologicals/areas/biological_therapeutics/Annex_3_WHO_TRS_1011_web-7.pdf?ua=1